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Economic Evaluation of Interventions in Parkinson's disease - A Systematic Literature Review

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Abstract

Background: Parkinson's disease (PD) management comprises of drug treatments, surgery and physical activity/occupational therapies to relieve PD's symptoms. The aim of this study is twofold; firstly, to appraise recent economic evaluation studies on PD management in order to update the existing knowledge and, secondly, to facilitate decision making on PD management by assessing the cost-effectiveness of all types of PD interventions.

Methods: A systematic search for studies published between 2010 and 2018 was conducted. The inclusion and exclusion of the articles were based on criteria relevant to Population, Intervention, Comparison, Outcomes and Study design (PICO). The reporting quality of the articles was assessed according to Consolidated Health Economic Evaluation Reporting Standards.

Results: Twenty eight articles were included, 10 of which were evaluations of drug treatments, 10 deep brain stimulation (DBS) and 8 physical/occupational therapies. Among early-stage treatments, Ti Ji dominated all physical activity interventions, however, its cost-effectiveness should be further explored in relation to its duration, intensity, and frequency. Multidisciplinary interventions of joint medical and non-medical therapies provided slightly better health outcomes for the same costs. In advanced PD patients, adjunct drug treatments could become more cost-effective if introduced during early PD and, although DBS was more cost-effective than adjunct drug therapies, the results were time-bound.

Conclusion: Conditionally, certain PD interventions are cost-effective. However, PD progression differs in each patient, thus the cost-effectiveness of individually-tailored combinations of interventions, which could provide more time in less severe disease states and improve patients' and caregivers' quality of life, should be further explored.

Background

Parkinson's disease (PD) is the second most common neurodegenerative disease, after Alzheimer's, which causes severe morbidity and mortality globally ¹ and leads to motor fluctuations, psychological and behavioral disorders. PD prevalence is estimated to affect nearly 1-2 per 1,000 people and is expected to double in the following 20-year timespan due to the intense demographic transition towards aging societies and extended life expectancy ². The number of people with PD in Europe will increase by 33% by 2030 and will reach 1.2 million people approximately in the USA by 2040³.

PD has major economic impacts on the patients, their families, and societies. Direct (medical, non-medical) and indirect (loss of productivity) PD costs in Europe reached €7.7 billion in 2010 ⁴. In the USA, each PD patient bears \$12,800 more medical expenses, expressed as healthcare visits and hospital inpatient days, and \$10,000 more non-medical costs including absenteeism/ presenteeism of patients and informal caregivers, than those with the same characteristics but without PD ³. The costs of informal caregivers comprise an important subgroup of the total costs and are often greater than direct costs ^{5,6}. Furthermore, since the vast majority of PD patients are in need of informal care, these costs pose a significant burden ⁷.

The causes of PD remain unknown; however, a combination of genetic and environmental factors possibly plays an important role in its genesis and progress ⁸. There is no cure for PD and existing treatments mainly relieve symptoms. Also, there is no early diagnostic test for PD so its diagnosis often occurs at a later stage after the symptoms have appeared ⁹. The most common and effective medication for PD symptomatology is levodopa ¹⁰. In its simplest form, oral levodopa has prolonged effect on increasing dopamine levels in the brain and restores movement functions ¹⁰. Apart from levodopa, Dopamine Agonists (DA) or MAO-B inhibitors (rasagiline and selegiline) can be used during the initial stages of PD¹¹.

Although oral levodopa conduces to long-lasting, adverse motor and psychological consequences, it could have short-term efficacy depending on its gastric absorption ¹². Thus, oral levodopa can be either replaced by continuous infusion therapies like subcutaneous

apomorphine and intraduodenal levodopa/carbidopa (Duodopa) or combined with MAO-B inhibitors and entacapone that can prolong levodopa's short half-life and boost its effectiveness^{10, 12-14}. DA appear similar negative side effects only when they are used as an adjunct to levodopa^{15, 16}.

As alternatives to drug therapies, surgical procedures, i.e. deep brain stimulation (DBS), stimulate the brain to decrease motor fluctuations in advanced PD patients¹⁷. DBS is based on the implantation of a medical device that induces electrical pulses to brain sites: the subthalamic nucleus (STN) or the globus pallidus internus (GPi). The pulses restore activity in neurons and improve patients' mobility and functionality while reducing medication use^{17, 18}. Besides the aforementioned interventions, there is also a positive effect of physical activity, occupational therapy and physiotherapy, complementary to drug treatment, on improving the motor and cognitive functions of PD patients in early stages^{12, 19-22}. Researchers are interested in interventions that can offer relief of the symptoms and can lead to sustainable and long lasting health outcomes².

Every intervention requires the utilization of scarce resources, thus economic evaluation is an expedient tool which facilitates decision making in regards to efficient use of resources²³. The bulk of economic evaluation studies in healthcare evaluate ways of allocating available resources in order to maximize population health²³. There are four main categories of economic evaluations; cost-effectiveness analysis (CEA), which measures outcomes in natural units and compares the efficiency of alternative interventions targeting the same objective. Cost-utility analysis (CUA) measures outcomes in utility units (QALYs or DALYs) and, since it compares the intervention to other interventions, it can be used for optimal spending decisions. Cost-benefit analysis (CBA) presents both outcomes and costs in monetary units and informs about the amount of societal resources needed to achieve a goal, and lastly cost-minimization analysis (CMA), which assumes equal outcomes and compares only the costs²³.

Current needs to ascertain PD interventions that provide the most efficient resource utilization (i.e. best outcomes for the occurring costs) imply constant reviews of the relevant

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economic evaluation studies. The systematic literature review is an effective method to identify the commonalities among the existing studies, highlight the knowledge gaps and provide recommendations for future research. There are several literature reviews of economic evaluations on PD^{10, 24-28} which do not include studies after 2010. The exception is the study by Becerra et al., which, however, does not include all types of interventions simultaneously²⁸. Thus, this paper has a twofold aim; to update the existing knowledge by appraising economic evaluations of PD interventions, and also to promote decision making on PD management by assessing the cost-effectiveness of all types of PD interventions.

Methodology

A systematic literature review was conducted for answering the research question in accordance with the PRISMA guidelines²⁹. Moreover, the Campbell and Cochrane Economics Methods Group guidelines³⁰ were followed for incorporating economic evidence including search criteria, data extraction, synthesis, and critical analysis.

Search strategy

A systematic search was performed to identify relevant articles published in both health economics and biomedical databases from 01.01.2010 till 31.12.2018. The databases searched were Medline (Pubmed), Embase and ECONbase, EconLit and Cumulative Index to Nursing and Allied Health (CINAHL) through Embase. Moreover, one additional database, the Centre for Reviews and Dissemination database was explored. We also searched the reference lists of the selected studies. A detailed search strategy including keywords is presented in the Supplemental materials (Supplemental Appendix 1).

Inclusion and exclusion criteria

After each search in the databases, the initial hits were exported into EndNote and duplicates were removed. The exclusion and inclusion of each study were based on the PICOS criteria which refer to the Population, Intervention, Comparison, Outcomes and Study design of an article (Supplemental Table 1). The inclusion criteria were referential to all types of economic evaluations (CEA, CUA, CMA, CBA) of any intervention for PD management,

including drug therapies, with no limitation regarding the comparator involving PD patients of any severity level. The retrieved studies were assessed in two phases; firstly, titles and abstracts were checked, according to PICOS, and thereafter, the full text of the remaining articles was screened for final selection.

Data extraction

The data from the selected studies was extracted regarding two dimensions; the study results (empirical evidence) and the methods (methodology). The reporting quality of the studies was assessed by using the CHEERS checklist³¹. The CHEERS checklist consists of 24 items divided into six main categories according to the articles' structure (title and abstract, introduction, methods, results, discussion, and other). For computing a final score, we assigned one point (1) if the item was complete and zero points (0) if the requirement was not fulfilled. In cases where the requirements were not applicable to the subject or structure of the study, we assigned Not Applicable (NA). The maximum score for reporting all items completely was 24 points. Finally, for ease of comparison, the extracted results were converted to US dollars in price year 2016³² and the local currency values are presented in parenthesis as exhibited in the studies. The cost is converted by using country-specific Gross Domestic Product (GDP) deflator indices to account for inflation. Thereafter, the price-year adjusted cost is converted to US dollars using Purchasing Power Parity rates³².

Results

Twenty eight studies were identified in the review. The detailed selection process of the studies is presented in Figure 1. The main characteristics of the selected studies are summarized in Supplemental Table 2. The categories and sources of costs as well as the measures and sources of QALYs, as these were reported in the selected studies, are presented in Supplemental Table 3. The subsequent interventions are divided into three main categories for ease of presentation and discussion: 1) drug treatments; 2) deep brain stimulation (DBS); and 3) other therapies focusing, mostly, on physical activity and occupational therapy. The cost-effectiveness results in the selected studies were presented either by incremental cost-effectiveness ratios (ICERs), *i.e.* the difference in costs between two alternatives divided by

the difference in outcomes of the two alternatives, or by reporting costs and outcomes in the intervention and comparator. The interventions are generally implemented according to the severity level of PD. PD severity is evaluated according to the Hoehn and Yahr (H&Y) staging scale which combines both disability and impairment by categorizing motor and balance/gait dysfunctions into 5 stages³³. Stage 1 represents the initial, least severe state and it is assumed that patients, starting from 1, progress to stage 5 as their status deteriorates³³.

Drug treatments

The most common treatment for counteracting the incipient symptoms of PD is oral monotherapy medication, *i.e.* levodopa, DA or rasagiline, which is effective in reducing motor fluctuations. In the USA, researchers compared the cost-effectiveness of rasagiline versus DA (ropinirole XL, pramipexole, generic ropinirole) or versus levodopa as initial therapies in PD³⁴. Treatment with rasagiline led to more QALYs (3.45 versus 3.34, 3.34, 3.34 for the DAs respectively, and 3.21 for levodopa), fewer patients with dyskinesia (38% and 73% respectively) and lower costs than ropinirole XL, pramipexole and levodopa, thus dominating the alternatives. Although rasagiline resulted in higher costs compared to generic ropinirole, it generated an ICER of \$28,406/QALY (\$25,939).

Ten patients in Norway underwent a before-after prospective study and shifted their treatment from oral levodopa to intestinal levodopa³⁵. The aim was to estimate whether this transition was cost-effective compared to maintaining the initial oral treatment. Intestinal levodopa had 0.047 higher QALY gain and approximately \$60,533 (472,000 NOK) higher costs compared to oral treatment, leading to \$1.18 million/QALY (NOK 9.2 million/QALY).

Levodopa/carbidopa intestinal gel (LCIG) was compared to standard treatment for PD patients from a healthcare perspective in Bulgarian, UK and Irish setting^{36 37, 38}. The 12 PD patients in Bulgaria exhibited improvement in UPDRS scores after the LCIG treatment with an ICER of \$3,050/QALY (1,904 BGN). In the UK and Irish study, a Markov model was used, over the lifetime, where patients remained in LCIG for the first five years and then returned back to standard treatment³⁸. The ICER was estimated at \$55,366/QALY (£36,024) in the UK and \$34,823/QALY (€26,944/QALY) in the Irish Study³⁶. However, the results of

these studies were relatively sensitive to patients' health state during the treatment initiation and to the duration of the health benefits. In a Swedish study, Duodopa's ICER compared to usual care amounted to \$776,408/QALY (SEK 6.1 million)³⁹. However, inclusion of non-medical costs, such as formal home help and informal care in the societal perspective, reduced the estimated ICER to \$54,730/QALY (SEK 430,000). A Markov model was used to compare continuous subcutaneous apomorphine to adjunct therapies (standard care), and to levodopa/carbidopa intestinal gel (LCIG) in the UK and Germany⁴⁰. LCIG dominated adjunct therapies over the lifetime in both countries. However, the ICER of LCIG compared to continuous subcutaneous apomorphine was \$355,169/QALY (£244,684) in the UK and \$350,000/QALY (€272,914) in Germany. Moreover, apomorphine's ICER over adjunct therapies in the UK was \$9347/QALY (£6440). Although apomorphine could limit some motor functions for the patients, the researchers suggested that, from a healthcare provider's perspective, it could be used as an alternative to adjunct therapies for patients not eligible to alternative treatments⁴⁰.

A CEA comparing prolonged release ropinirole (PR) versus immediate-release ropinirole (IR) was conducted for PD patients in the Netherlands⁴¹. Both drugs were used complementary to levodopa treatment. In the Markov model, the health states were based on the H&Y stages and the transition among these states could be performed in six-month cycles. The analyses, both short-term (5 years) and over lifetime, were performed from a healthcare providers' perspective and only direct costs were included, i.e. drug costs, costs for elderly care and hospital care. PR was dominant over IR, with a QALY gain of 0.08 in the short-term and 0.24 in the long-term and reduced the costs of \$25,444 (€19,700) and \$52,050 (€40,300) over 7- and 10-years period, respectively. However, indirect costs and outcomes were not considered, thus, an intimate apprehension was not possible.

In one CUA, three different treatment combinations were compared to standard care (levodopa monotherapy) in the USA⁴². The treatments were rasagiline+levodopa (RAS+LD), entacapone+ levodopa (ENT+LD), and levodopa/ carbidopa/entacapone (LCE). A 2-year Markov model was used where patients moved to different health states in every four months. The transition probabilities, cost, and health utilities were derived from various clinical trials

and the cost-effectiveness was investigated from both the societal and payer perspective. In both perspectives, RAS+LD and LCE had greater effectiveness, compared to levodopa. From a societal perspective, ENT+LD led to \$13,340/QALY (\$12,031), compared to levodopa. The indirect costs, caregiver's costs as well as patients' heterogeneity were not included. Furthermore, no sensitivity analysis was conducted. Francois et al.⁴³ used a Markov model to explore the cost-effectiveness of droxidopa (6 months) followed by standard care (6 months) versus 12 months of standard care, from a payer perspective in the USA. The ICER was \$47,528/QALY (\$47,001/QALY).

Deep Brain Stimulation

A Markov model was used to determine cost-effectiveness of DBS plus best medical treatment compared to best/standard medical treatment alone in two studies in the UK^{44 45}, in Germany⁴⁶ and in the USA⁴⁷. The time frame for the studies was 5 years, 15 years⁴⁵, lifetime⁴⁶ and 10 years⁴⁷. All the studies defined patients' health state according to the H&Y stages, and the cycle lengths were one year^{44 45} and 6 months^{46, 47}. Costs of surgery, battery replacement, and the cost of the adverse events were the main contributors to the total costs. The ICERs for the treatment options were \$31,780/QALY (£20,678)⁴⁴, \$28,867/QALY (£19,887/QALY)⁴⁵, \$9,333/QALY (€6,700/QALY)⁴⁶ and \$23,870/QALY (\$23,404/QALY)⁴⁷. The results were sensitive to patients' H&Y stage. This was further elaborated in a study from Japan where CUA was performed considering different PD stages of the patients (early, intermediate, late)⁴⁸. Using a Markov model, they showed that the ICER varied from \$29442/QALY (\$70,200/QALY) in the early, increased to \$26110/QALY (\$25,600/QALY) in the intermediate and dropped to \$27,742/QALY (\$27,200/QALY) in the late over the 10 years from a healthcare perspective.

A similar study was conducted in Hong Kong, where DBS was compared with standard medical treatment by following 13 patients having DBS surgery over two years⁴⁹. The standard care cost was estimated before the surgery. For the two-year period, the ICER was \$134,821/QALY (\$123,110) in the first year and \$68,824/QALY (\$62,846) in the second

year. The cost was higher in the first year due to DBS surgery but reduced substantially in the next year. The authors suggested that the procedure might have been even more cost-effective during the following years, however, the sample size was relatively small⁴⁹. DBS was reported cost-effective compared to standard care⁴⁰ but dominated by continuous subcutaneous apomorphine in both the UK and Germany⁴⁰ as described in the Drug treatment section.

In two studies, the cost-effectiveness of DBS procedure in two different sites; globus pallidus internus (GPi) and subthalamic nucleus (STN), was compared^{50, 51}. The first study was a CMA which compared the medication costs before and after the surgery, and between the GPi and STN approaches. The medication costs were significantly lower for both sites compared to best medical treatment, and STN had significantly lower costs compared to GPi⁵⁰. In the second study, the medication costs of STN were also lower compared to GPi. The ICER of GPi versus STN stimulation was \$109,901/QALY (\$100,355) from a provider's perspective and \$59,280/QALY (\$54,129) from a societal perspective⁵¹. Using a previously used Markov model⁴⁴, Dams et al⁵² showed that of STN DBS plus BMT had ICER \$30,316.81/QALY (€22,710/QALY) comparing to BMT alone in Germany over the lifetime of 251 young PD patients. Only one study was performed alongside an RCT, the PD SURG trial in the UK⁵³. The ICER was \$735,200/QALY (£468,528/QALY) at year one and was interpreted as not cost-effective from a health and social care perspective but the extrapolation of costs and outcomes in the DSA over 5 years resulted in a lower ICER \$91,272/QALY (£45,180/QALY).

Other therapies

Cost-effectiveness of a physical exercise program was explored compared to usual care in Australia from a health system's perspective⁵⁴. Both CEA and CUA were conducted where the outcomes for CEA were fall prevention and prevention of mobility deterioration, and for the CUA the outcome was QALYs. Fall rates had decreased among patients 6 months post-intervention. The ICERs were \$408/fall prevented (AUD 574), \$6,810/person avoiding mobility deterioration (AUD 9,570) and \$241,097/QALY (AUD 338,800). In a UK study, no

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differences in effect (fall prevention) or costs were observed for an exercise trial. The duration was 20 weeks and the comparator was usual care ⁵⁵.

Fall prevention was also evaluated in an American study of Ti Ji Quan for PD patients ⁵⁶. The secondary outcome was QALY. Ti Ji Quan is a balance-based exercise, this was compared to both resistance training and stretching. The Ti Ji Quan participants had a lower number of falls and significantly higher QALY than both resistance training and stretching groups during the 9-month period. The calculated ICER of Ti Ji Quan was \$3,641/QALY (\$3,394). However, the long-term cost-effectiveness of the intervention was not observed, and informal caregivers' costs were not included ⁵⁶. In a Dutch setting, an evidence-based physiotherapy community program was assessed, compared to usual physiotherapy, as a complementary treatment to drug therapy ⁵⁷. Main outcomes were patients' improvement in mobility and mobility-related quality of life. Although no differences were observed between the two groups in terms of health outcomes, the total costs were \$939 (€727) lower in the intervention group. The largest cost saving in the intervention group was due to reduced informal care costs \$404 (€13).

The cost-effectiveness of a home-based occupational therapy program for PD patients and their caretakers in the Netherlands was compared with a control group receiving usual care. The CUA was conducted alongside a randomized controlled trial ⁵⁸. There were insignificant differences in costs between the two groups irrespectively of inclusion or exclusion of informal care. The only significant difference was the lower institutional costs for the intervention group (\$1,516/€1,458). The intervention group of patients and caregivers gained 0.02 and 0.04 QALYs respectively over the 6-month trial period. Occupational therapy combined with physiotherapy was also compared with no therapy in the UK⁵⁹. The CUA was performed alongside RCT in patients with moderate PD (H&Y 3). The ICER was \$5,282.64/QALY (£3,493/QALY).

In a Dutch study, 301 PD patients either participated in a multidisciplinary intervention or served as control following their usual care ⁶⁰. The intervention included an assessment from a multidisciplinary team and guidance on both pharmacological and non-pharmacological

therapies. The results showed that activities of daily living and quality of life (QoL) were slightly higher in the intervention group over the 8-month follow up (1.3 and 3.0 points respectively) while no differences were noted for motor outcomes or overall caregivers' burden. No statistically significant differences in costs were observed.

A CEA alongside RCT examined the cost-effectiveness of home-based motor monitoring plus standard in-office visits (HBMM) comparing to in-office visits alone for advanced PD patients in Spain⁶¹. The outcomes were UPDRS (I, II, III, IV) and QALYs and were examined from a healthcare perspective, throughout 1 year. The HBMM was cost-effective considering UPDRS outcome i.e. \$191.20/UPDRS unit (€126.72/UPDRS unit) but not cost-effective considering QALY.

Discussion

This systematic literature review evaluated all available evidence on the cost-effectiveness of treatment/interventions for PD patients to enrich the existing literature. Although the cost-effectiveness of all types of PD interventions was evaluated, our findings regarding the key role of time horizon in defining the cost-effectiveness as well as the importance of early treatment initiation coincide with previous reviews^{10, 28}.

Although the interventions included in this review were very heterogeneous, the comparability of cost-effectiveness results across the three categories of PD interventions was determined by various key factors, i.e. the types of analyses and comparators of treatments, the efficacy of interventions, the perspectives, the existing reimbursement mechanisms, and the diverse instruments for assessing effectiveness. Taking into account the existing diversification in acceptable willingness-to-pay threshold ranges; NICE's threshold varies from £20,000 to £30,000/QALY gained^{51, 52}, the American literature mentions \$50,000/QALY⁶² and in Australian studies AUD50,000/DALY is used⁵⁴, the cost-effectiveness results may differ in terms of generalizability and applicability across settings.

In this review, NICE's threshold is considered for determining the cost-effectiveness of PD interventions (\$33,022- \$49,533).

For ease of discussion, we categorize PD management in two main tiers as identified by NICE; management of early PD (initial functional effects of the disease) and management of late PD (motor implications)⁶³. Standard care or best medical treatment, including mostly oral levodopa, was used as the main comparator across interventions, which eased the comparability of the outcomes. However, there were studies that compared the results within the same category of interventions^{34, 35, 37, 38, 40-42, 50, 51, 56}.

Management of early PD

Initial drug treatments and physical and occupational therapy were used in this stage. The contribution of physical activity and occupational therapy, in addition to usual treatment, is limited as most differences between the intervention and the control group in costs and outcomes were statistically insignificant^{55, 58, 59}. When QALYs were measured by the EQ-5D scale for physical exercise there were no significant differences in the outcomes^{55, 59}, and although a positive effect noted when measured by the SF-6D scale, the intervention was not cost-effective (ICER \$241,097/QALY)⁵⁴. It is known that SF-6D is more sensitive in detecting differences in patients' health-status, disability and medication use than EQ-5D⁶⁴.

Ti Ji provided better results compared to other types of physical activity despite a variation in its cost-effectiveness. The variation derives from the use of different types of analysis; CEA which used natural units (falls prevented) to measure the outcome and CUA which used the utility measure of QALYs for the outcome. It is widely argued that CEA is more relevant to clinicians since the preferred type of outcome measure is therapeutic units⁶⁵. CUA is preferred to facilitate decision-making and increase the comparability of results⁶⁶.

Nevertheless, the QALY underestimates the gains of short-term palliative care interventions and is not well suited to capture symptom improvements in elderly PD populations with a short lifespan⁶⁷. Hence, QALY-based results should be treated with caution since they could facilitate poor decision making that would, only, serve the needs of younger populations being in the early stages of the disease. Aiming at more robust findings, the long-term cost-

effectiveness of Ti Ji needs to be further explored in correlation to the duration, intensity, and frequency of the activities ^{68, 69}.

Multidisciplinary interventions, of combined drug treatments and non-medical therapy, when practiced in early stages led to minor improvements in QoL with the same costs ⁶⁰. Indeed, multidisciplinary therapies help patients remain functional in their everyday life for a longer period, thus, not needing institutionalization or informal care ⁷⁰. Institutional costs, transport and caregivers' time are important categories of expenses for this type of interventions ⁷⁰.

Management of late PD

PD management in the advanced stages prioritizes adjunct or continuous infusion drug therapies and surgery for soothing patients' motor impairments. Continuous subcutaneous apomorphine was more cost-effective from the healthcare perspective and adjunct treatments appeared more cost-effective in the societal perspective. In the UK, non-oral treatments in advanced PD patients led to reduced healthcare costs, compared to oral therapy, expressed as 28% less non-elective admissions to the hospital ⁷¹. We find that apomorphine is dominant among non-oral treatments from a healthcare perspective ⁴⁰. However, when apomorphine was compared to levodopa/carbidopa intestinal gel the results varied according to the setting as the ICER was lower in the UK (\$9,350) than in Germany (\$108,423) ⁴⁰. A possible explanation is that PD drug costs per patient in Germany amount to approximately €1,520 whereas in the UK drug costs are considered the smallest component of the total costs of the disease ^{72, 73}. Adjunct treatments can relieve motor symptoms and reduce adverse side effects leading to cost savings and long-term improvements in patients' QoL ⁷. Prolonged time without motor symptoms lengthens patients' mobility and lightens the burden on informal caregivers ⁷⁴. While patients could also enjoy the benefits of this moderate symptom progression earlier by initiating adjunct treatments in the initial stages, prescription rates of single-drug therapies continue to be higher than those of adjunct drug treatment in early PD. The official guidelines of NICE and the Canadian Guidelines on Parkinson's Disease, still, suggest monotherapy as the initial pharmacological therapy in PD patients ^{75, 76}. Accordingly, prescription patterns in the USA show that almost 80% of newly treated PD patients receive

single drug treatment⁷⁷. Adjunct treatments were cost-effective from a societal perspective, however, informal caregivers' costs and QoL were wrongly excluded from one analysis⁴², which, if avoided, might have indicated greater societal benefits.

DBS was dominated by apomorphine but was more cost-effective than adjunct and standard drug treatments from a healthcare perspective leading to decreased medication use and a prolonged state of mild motor symptoms^{40, 44-46, 52}. According to McIntosh, a latent cost-saving effect of DBS derives from the subsequent reduction of medication use among patients⁷⁸. Time was an integral factor in the cost-effectiveness of DBS. Firstly, taking into account the progressive nature of PD, there is a clear association between undertaking DBS in early age (60 years) and greater cost-effectiveness (\$4,740/QALY)^{46, 48}. Secondly, the costs were particularly bound to the time horizon followed, with greater reductions observed after the first year of surgery^{49, 53}. The findings from CUA alongside RCT stated that DBS was not considered cost-effective at first year \$735,200/QALY (£468,528/ QALY) which is also confirmed by extrapolation analysis but its ICER was expected to fall under accepted thresholds in a five-year timespan⁵³. This variation could be attributed to expensive medical equipment, maintenance costs and hospitalization due to surgery^{28, 78}. However, it is worth to mention that the QALY information measured by EQ-5D for DBS patients are limited in many studies. Only one study (the PD SURG trial) had patient level data but was limited for first year only⁵³. One-year QALY data was extrapolated for 10 years in this study.

The ICER of GPi versus STN is higher than the acceptable WTP range but STN DBS was cost-effective comparing to BMT⁵². In terms of the health outcome there is no conclusive evidence for the optimal site, thus researchers suggested a patient-tailored evaluation by a multidisciplinary professional team for choosing the DBS site⁷⁹. Nevertheless, STN had comparatively lower costs than GPi⁵⁰.

Disease severity and funding source

The observed trends of costs and outcomes showed that the costs ascended and QoL descended sequentially at the severe state of PD (H&Y 4.0-5.0)^{38, 41, 44, 48} which is in line with previous studies^{6, 25, 80, 81}. Therefore, greater cost-effectiveness can be achieved in

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interventions that are initiated at an early stage than later. Furthermore, the majority of studies referring to drug treatments and surgery was funded by pharmaceutical companies and only those including physical activity/occupational therapy and multidisciplinary interventions were funded by the government or non-governmental organizations (Supplemental Table 2). Generally, caution is advised in the interpretation of studies funded by industry, as these studies have been shown to be more prone to report favorable cost-effectiveness ratios⁸² and in the case of model-based studies, the findings tend to be even more problematic⁸³.

Reporting quality assessment

The quality of reporting was insufficient for several articles, despite the fact that guidelines for conducting economic evaluations are available. Several items were partially reported or missing in some articles, including a proper description of costing methods such as unit costs, sources of costs items (registers or data from other countries), timing of the cost collection (prospectively or retrospectively), and methods to transform the costs from one country to another country. Taking into account that the CHEERS guidelines were published in 2013, studies published earlier than 2013 had a lower mean score (19.33) than those published in 2013 and later (20.33). It is possible that the CHEERS statement has improved the reporting quality and we suggest that it should be habitually employed for further improvements in reporting.

Limitations

This study is not free of limitations. In this review, we investigated all types of intervention that were provided to PD patients. On one hand, the reader is presented with a comprehensive overview of drug interventions, DBS and other types of intervention which could be seen as a strength of this review. On the other hand, methodological differences between the interventions may have prevented in a precise way which types of interventions are most cost-effective. Thus, our broad approach could also be seen as a weakness. Moreover, as the reporting quality of the articles according to CHEERS was based on personal interpretations, disagreement may arise about each study's score. In fact, a quality assessment of modeling

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studies using different checklists would have been interesting⁸⁴. Furthermore, we have not assessed the methodological quality of the articles, especially for the simulation models and we did not perform a systematic quantitative assessment to identify key drivers of the cost-effectiveness.

Conclusion

Tailoring PD management according to the subsequent cost-effectiveness of PD interventions should consider the absence of the cure and the progressive nature of the disease. Under certain restrictions, Ti Ji and multidisciplinary interventions seem to be more cost-effective for early PD management. In advanced PD, apomorphine was considered cost-effective from a healthcare perspective and adjunct treatments from a societal perspective. DBS presented cost-effectiveness in the long-term. However, PD progression differs depending on patients' individual characteristics, levels and quality of informal care as well as disease severity. Hence, further research on the cost-effectiveness of individually-tailored combinations of existing PD interventions, with respect to patients' own circumstances, is needed in order to be able to draw more robust conclusions about optimal PD management.

Authors' roles:

Nafsika Afentou:

- 1) Analysis: Design, Execution
- 2) Manuscript: Writing

Ulf Gerdtham:

- 1) Manuscript: Review and Critique

Johan Jarl:

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Sanjib Saha:

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The authors declare that there are no additional disclosures to report.

Ethical Compliance Statement:

The authors confirm that the approval of an institutional review board / patient consent was not required for this work.

Informed patient consent was not necessary for this work.

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

References:

1. de Lau LML, Breteler MMB. Epidemiology of Parkinson's disease. *The Lancet Neurology* 2006;5(6):525-535.
2. Tinelli, Kanavos P, Grimaccia F. The value of early diagnosis and treatment in parkinson's disease:A literature review of the potential clinical and socioeconomic impact of targeting unmet needs in Parkinson's disease. London: The London School of Economics and Political Science; 2016.
3. Kowal SL, Dall TM, Chakrabarti R, Storm MV, Jain A. The current and projected economic burden of Parkinson's disease in the United States. *Movement Disorders* 2013;28(3):311-318.
4. Gustavsson A, Svensson M, Jacobi F, et al. Cost of disorders of the brain in Europe 2010. *European Neuropsychopharmacology* 2011;21:718-779.
5. Céu M, Coloma J. Health Economics and Cost of Illness in Parkinson's Disease. *Movement Disorders* 2013;8(1):6-9.
6. McCrone P, Allcock LM, Burn DJ. Predicting the cost of Parkinson's disease. *Movement Disorders* 2007;22(6):804-812.
7. von Campenhausen S, Winter Y, Rodrigues e Silva A, et al. Costs of illness and care in Parkinson's Disease: An evaluation in six countries. *European Neuropsychopharmacology* 2011;21(2):180-191.
8. Wirdefeldt K, Adami H-O, Cole P, Trichopoulos D, Mandel J. Epidemiology and etiology of Parkinson's disease: a review of the evidence. *European Journal of Epidemiology* 2011;26(1):1.
9. Pahwa R, Lyons K. Early diagnosis of Parkinson's disease: recommendations from diagnostic. *Am J Manag Care* 2010:S94-99.
10. Cubo E. Pharmacotherapy in the management of early Parkinson's disease: cost-effectiveness and patient acceptability. *ClinicoEconomics and outcomes research : CEOR* 2010;2:127-134.
11. Riederer P, Laux G. MAO-inhibitors in Parkinson's Disease. *Experimental neurobiology* 2011;20(1):1-17.
12. Clarke CE, Worth P, Grosset D, Stewart D. Systematic review of apomorphine infusion, levodopa infusion and deep brain stimulation in advanced Parkinson's disease. *Parkinsonism & Related Disorders* 2009;15(10):728-741.
13. Rascol O, Brooks DJ, Melamed E, et al. Rasagiline as an adjunct to levodopa in patients with Parkinson's disease and motor fluctuations (LARGO, Lasting effect in Adjunct therapy with Rasagiline Given Once daily, study): a randomised, double-blind, parallel-group trial. *The Lancet* 2005;365(9463):947-954.
14. Zhuo C, Ji F, Zhu X, et al. Comparison for Efficacy and Tolerability among Ten Drugs for Treatment of Parkinson's Disease: A Network Meta-Analysis. *Scientific Reports* 2017;8.
15. Markham C, Diamond S. Long-term follow-up of early dopa treatment in Parkinson's disease. *Annals of neurology* 1986: 365–372.

16. BROOKS DJ. Dopamine agonists: their role in the treatment of Parkinson's disease. *Journal of Neurology, Neurosurgery & Psychiatry* 2000;68(6):685-689.
17. Ludovico I, Damborská A. Deep Brain Stimulation in Parkinson's Disease:. *Activitas Nervosa Superior* 2017;4-11.
18. Perestelo-Pérez L, Rivero-Santana A, Pérez-Ramos J, Serrano-Pérez P, Panetta J, Hilarion P. Deep brain stimulation in Parkinson's disease: meta-analysis of randomized controlled trials. *Journal of Neurology* 2014;261(11):2051-2060.
19. Lauzé M, Daneault J-F, Duval C. The Effects of Physical Activity in Parkinson's Disease: A Review. *Journal of Parkinson's Disease* 2016;6(4):685-698.
20. Goodwin VA, Richards SH, Taylor RS, Taylor AH, Campbell JL. The effectiveness of exercise interventions for people with Parkinson's disease: a systematic review and meta-analysis. *Movement disorders : official journal of the Movement Disorder Society* 2008;23(5):631-640.
21. Tomlinson CL, Patel S, Meek C, et al. Physiotherapy intervention in Parkinson's disease: systematic review and meta-analysis. *BMJ : British Medical Journal* 2012;345.
22. Shen X, Wong-Yu ISK, Mak MKY. Effects of Exercise on Falls, Balance, and Gait Ability in Parkinson's Disease. *Neurorehabilitation and Neural Repair* 2016;30(6):512-527.
23. Drummond MF, Sculpher MJ, Claxton K, Stoddart GL, Torrance GW. *Methods for the economic evaluation of health care programmes*: Oxford : Oxford University Press, 2015.
- Fourth edition / Michael F. Drummond, Mark J. Sculpher, Karl Claxton, Greg Stoddart, George W. Torrance., 2015.
24. Rubenstein LM, deLeo A, Chrischilles EA. Economic and Health-Related Quality of Life Considerations of New Therapies in Parkinson's Disease. *Pharmacoeconomics* 2001;19(7):729.
25. Dowding CH, Shenton CL, Salek SS. A Review of the Health-Related Quality of Life and Economic Impact of Parkinson's Disease. *Drugs & aging* 2006;23(9):693-721.
26. Eggert KM, Reese JP, Oertel WH, Dodel R. Cost effectiveness of pharmacotherapies in early Parkinson's disease. *CNS Drugs* 2008;22(10):841-860.
27. Siderowf AD, Holloway RG, Stern MB. Cost-effectiveness analysis in Parkinson's disease: determining the value of interventions. *Movement Disorders: Official Journal Of The Movement Disorder Society* 2000;15(3):439-445.
28. Becerra JE, Zorro O, Ruiz-Gaviria R, et al. Economic Analysis of Deep Brain Stimulation in Parkinson Disease: Systematic Review of the Literature. *World Neurosurgery* 2016;93:44-49.
29. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA StatementThe PRISMA Statement. *Annals of Internal Medicine* 2009;151(4):264-269.
30. Higgins JP, Green S. *Cochrane handbook for systematic reviews of interventions*: Wiley Online Library, 2008.
31. Husereau et al. D. Consolidated Health Economic Evaluation Reporting Standards (CHEERS)—Explanation and Elaboration: A Report of the ISPOR Health Economic Evaluation Publication Guidelines Good Reporting Practices Task Force. *Value In Health* 2013;231-250.

- Accepted Article
32. Shemilt I, Thomas J, Morciano M. A web-based tool for adjusting costs to a specific target currency and price year. *Evidence & Policy: A Journal of Research, Debate and Practice* 2010;6(1):51-59.
 33. Goetz CG, Poewe W, Rascol O, et al. Movement Disorder Society Task Force report on the Hoehn and Yahr staging scale: status and recommendations. *Movement Disorders: Official Journal Of The Movement Disorder Society* 2004;19(9):1020-1028.
 34. Farkouh RA, Wilson MR, Tarrant ML, Castelli-Haley J, Armand C. Cost-effectiveness of rasagiline compared with first-line early Parkinson disease therapies. *American Journal of Pharmacy Benefits* 2012;4(3):99-107.
 35. Lundqvist C, Beiske AG, Reiertsen O, Kristiansen IS. Real life cost and quality of life associated with continuous intraduodenal levodopa infusion compared with oral treatment in Parkinson patients. *Journal of Neurology* 2014;261(12):2438-2445.
 36. Lowin J, Sail K, Baj R, et al. The cost-effectiveness of levodopa/carbidopa intestinal gel compared to standard care in advanced Parkinson's disease. *J Med Econ* 2017;20(11):1207-1215.
 37. Kamusheva MS, Gerasimov N, Petrova GI. Intestinal gel Levodopa + Carbidopa in Parkinson's patients with frequent and prolonged akinesia - an economic evaluation. *International Journal of Pharmaceutical Sciences Review and Research* 2013;22(1):244-246.
 38. Lowin J, Bergman A, Chaudhuri KR, et al. A cost-effectiveness analysis of levodopa/carbidopa intestinal gel compared to standard care in late stage Parkinson's disease in the UK. *Journal of medical economics* 2011;14(5):584-593.
 39. Willis M, Persson U, Zoellner Y, Grادل B. Reducing uncertainty in value-based pricing using evidence development agreements: the case of continuous intraduodenal infusion of levodopa/carbidopa (Duodopa) in Sweden. *Applied health economics and health policy* 2010;8(6):377-386.
 40. Walter E, Odin P. Cost-effectiveness of continuous subcutaneous apomorphine in the treatment of Parkinson's disease in the UK and Germany. *Journal of Medical Economics* 2015;18(2):155-165.
 41. van Boven JFM, Novak A, Driessen MT, Boersma C, Boomsma MM, Postma MJ. Economic Evaluation of Ropinirole Prolonged Release for Treatment of Parkinson's Disease in The Netherlands. *Drugs & Aging* 2014;31(3):193-201.
 42. Groenendaal H, Tarrant ML, Armand C. Treatment of Advanced Parkinson's Disease in the United States A Cost-Utility Model. *Clinical Drug Investigation* 2010;30(11):789-798.
 43. Francois C, Hauser RA, Aballea S, Dorey J, Kharitonova E, Hewitt LA. Cost-effectiveness of droxidopa in patients with neurogenic orthostatic hypotension: post-hoc economic analysis of Phase 3 clinical trial data. *J Med Econ* 2016;19(5):515-525.
 44. Eggington S, Valdeoriola F, Chaudhuri KR, Ashkan K, Annoni E, Deuschl G. The cost-effectiveness of deep brain stimulation in combination with best medical therapy, versus best medical therapy alone, in advanced Parkinson's disease. *Journal of Neurology* 2014;261(1):106-116.
 45. Fundament T, Eldridge PR, Green AL, et al. Deep Brain Stimulation for Parkinson's Disease with Early Motor Complications: A UK Cost-Effectiveness Analysis. *PLoS One* 2016;11(7):e0159340.

- Accepted Article
46. Dams J, Siebert U, Bornschein B, et al. Cost-effectiveness of deep brain stimulation in patients with Parkinson's disease. *Movement Disorders* 2013;28(6):763-771.
 47. Pietzsch JB, Garner AM, Marks WJ, Jr. Cost-Effectiveness of Deep Brain Stimulation for Advanced Parkinson's Disease in the United States. *Neuromodulation : journal of the International Neuromodulation Society* 2016;19(7):689-697.
 48. Kawamoto Y, Mouri M, Taira T, Iseki H, Masamune K. Cost-Effectiveness Analysis of Deep Brain Stimulation in Patients with Parkinson's Disease in Japan. *World Neurosurg* 2016;89:628-635.e621.
 49. Zhu XL, Chan DTM, Lau CKY, et al. Cost-Effectiveness of Subthalamic Nucleus Deep Brain Stimulation for the Treatment of Advanced Parkinson Disease in Hong Kong: A Prospective Study. *World Neurosurgery* 2014;82(6).
 50. Weaver FM, Stroupe KT, Cao L, et al. Parkinson's disease medication use and costs following deep brain stimulation. *Movement Disorders* 2012;27(11):1398-1403.
 51. Stroupe KT, Weaver FM, Cao L, et al. Cost of Deep Brain Stimulation for the Treatment of Parkinson's Disease by Surgical Stimulation Sites. *Movement Disorders* 2014;29(13):1666-1674.
 52. Dams J, Balzer-Geldsetzer M, Siebert U, et al. Cost-effectiveness of neurostimulation in Parkinson's disease with early motor complications. *Movement disorders : official journal of the Movement Disorder Society* 2016;31(8):1183-1191.
 53. McIntosh E, Gray A, Daniels J, et al. Cost-utility analysis of deep brain stimulation surgery plus best medical therapy versus best medical therapy in patients with Parkinson's: Economic evaluation alongside the PD SURG trial. *Movement disorders : official journal of the Movement Disorder Society* 2016;31(8):1173-1182.
 54. Farag I, Sherrington C, Hayes A, et al. Economic evaluation of a falls prevention exercise program among people With Parkinson's disease. *Movement Disorders* 2015;31(1):53-61.
 55. Fletcher E, Goodwin VA, Richards SH, Campbell JL, Taylor RS. An exercise intervention to prevent falls in Parkinson's: an economic evaluation. *Bmc Health Services Research* 2012;12.
 56. Li F, Harmer P. Economic Evaluation of a Tai Ji Quan Intervention to Reduce Falls in People With Parkinson Disease, Oregon, 2008-2011. *Preventing Chronic Disease* 2015;12:E120.
 57. Munneke M, Nijkrake MJ, Keus SH, et al. Efficacy of community-based physiotherapy networks for patients with Parkinson's disease: a cluster-randomised trial. *Lancet Neurology* 2010;9(1):46-54.
 58. Sturkenboom IHW, Hendriks JCM, Graff MJL, et al. Economic evaluation of occupational therapy in Parkinson's disease: A randomized controlled trial. *Movement Disorders* 2015;30(8):1059-1067.
 59. Clarke CE, Patel S, Ives N, et al. Clinical effectiveness and cost-effectiveness of physiotherapy and occupational therapy versus no therapy in mild to moderate Parkinson's disease: a large pragmatic randomised controlled trial (PD REHAB). *Health Technol Assess* 2016;20(63):1-96.

60. van der Marck MA, Munneke M, Mulleners W, et al. Integrated multidisciplinary care in Parkinson's disease: a non-randomised, controlled trial (IMPACT). *Lancet Neurology* 2013;12(10):947-956.
61. Cubo E, Mariscal N, Solano B, et al. Prospective study on cost-effectiveness of home-based motor assessment in Parkinson's disease. *Journal of telemedicine and telecare* 2017;23(2):328-338.
62. Weinstein MC. How much are Americans willing to pay for a quality-adjusted life year? *Med Care* 2008;46(4):343-345.
63. NICE. Parkinson's disease in adults-NICE guideline. <https://www.nice.org.uk/guidance/NG712017>.
64. Petrou S, Hockley C. An investigation into the empirical validity of the EQ-5D and SF-6D based on hypothetical preferences in a general population. *Health Economics* 2005;14(11):1169-1189.
65. Gold M, Siegel J, Russell L, Weinstein M. *Cost-Effectiveness in Health and Medicine*. New York: Oxford University Press, 1996.
66. Jakubiak-Lasocka J, Jakubczyk M. Cost-effectiveness versus Cost-Utility Analyses: What Are the Motives Behind Using Each and How Do Their Results Differ?-A Polish Example. *Value in Health Regional Issues* 2014;4:66-74.
67. Pettitt D, Raza, S, Naughton, B et al., The limitations of QALY: a literature review. . *Journal of Stem Cell Research and Therapy* 2016;6(4):1-7.
68. Amano S, Nocera JR, Vallabhajosula S, et al. The effect of Tai Chi exercise on gait initiation and gait performance in persons with Parkinson's disease. *Parkinsonism & Related Disorders* 2013;19(11):955-960.
69. Ransmayr G. Physical, occupational, speech and swallowing therapies and physical exercise in Parkinson's disease. *Journal of Neural Transmission* 2011;118(5):773-781.
70. Gage H, Kaye J, Owen C, Trend P, Wade D. Evaluating rehabilitation using cost-consequences analysis: an example in Parkinson's disease. *Clinical Rehabilitation* 2006;20(3):232-238.
71. Heald AH, Livingston M, Stedman M, Wyrko Z. Higher levels of apomorphine and rotigotine prescribing reduce overall secondary healthcare costs in Parkinson's disease. *International Journal of Clinical Practice* 2016;70(11):907-915.
72. Findley LJ, Wood E, Lowin J, Roeder C, Bergman A, Schiffers M. The economic burden of advanced Parkinson's disease: an analysis of a UK patient dataset. *Journal of medical economics* 2011;14(1):130-139.
73. Spottke AE, Reuter M, Machat O, et al. Cost of illness and its predictors for Parkinson's disease in Germany. *Pharmacoeconomics* 2005;23(8):817-836.
74. Krol M, Papenburg J, van Exel J. Does Including Informal Care in Economic Evaluations Matter? A Systematic Review of Inclusion and Impact of Informal Care in Cost-Effectiveness Studies. *Pharmacoeconomics* 2015;33(2):123-135.
75. Canadian Guidelines on Parkinson's Disease executive summary. *The Canadian Journal of Neurological Sciences / Le Journal Canadien Des Sciences Neurologiques* 2012;39(4, Suppl 4):S1-S30.
76. Conditions NCCfC. Parkinson's disease: national clinical guideline for diagnosis and management in primary and secondary care. . London2006.

77. Huse DM, Castelli-Haley J, Orsini LS, Lenhart G, Abdalla JA. Patterns of initial pharmacotherapy for Parkinson's disease in the United States. *Journal Of Geriatric Psychiatry And Neurology* 2006;19(2):91-97.
78. McIntosh E. Perspective on the Economic Evaluation of Deep Brain Stimulation. *Frontiers in Integrative Neuroscience* 2011;5(19).
79. Mirza S, Yazdani U, Dewey Iii R, et al. Comparison of Globus Pallidus Interna and Subthalamic Nucleus in Deep Brain Stimulation for Parkinson Disease: An Institutional Experience and Review. *Parkinson's Disease* 2017;2017:3410820.
80. Keränen T, Kaakkola S, Sotaniemi K, et al. Economic burden and quality of life impairment increase with severity of PD. *Parkinsonism and Related Disorders* 2003;9:163-168.
81. Winter Y, von Campenhausen S, Brozova H, et al. Costs of Parkinson's disease in eastern Europe: a Czech cohort study. *Parkinsonism Relat Disord* 2010;16(1):51-56.
82. Bell CM, Urbach DR, Ray JG, et al. Bias in published cost effectiveness studies: systematic review. *Bmj* 2006;332(7543):699-703.
83. Garattini L, Koleva D, Casadei G. Modeling in pharmacoeconomic studies: Funding sources and outcomes. *International Journal of Technology Assessment in Health Care* 2010;26(3):330-333.
84. Caro JJ, Briggs AH, Siebert U, Kuntz KM. Modeling good research practices—overview a report of the ISPOR-SMDM modeling good research practices task force–1. *Medical Decision Making* 2012;32(5):667-677.

Figure 1: PRISMA flow chart for the selection of studies

